REMARKS

Claims 1-21 are pending in the present application. Reconsideration of the application is respectfully requested in view of the following responsive remarks. For the Examiner's convenience and reference, Applicant's remarks are presented in the order in which the corresponding issues were raised in the Office Action.

In the office action of October 3, 2006, the following actions were taken:

(1) Claims 1-21 were rejected under 35 U.S.C. 103(a) as being obvious in view of the combination of Grissom et al. US Pat. No. 6,797,521 (hereinafter "Grissom"), J. Org. Chem. (2002), Vol. 67, pages 1866-1872 (hereinafter "Toki"), Bioorganic & Medicianl Chemistry Letters (1998), Vol. 8, pages 3341-3346 (hereinafter "Dubowchik"), and US Pat. No. 5,574,018 (hereinafter "Habberfield").

It is respectfully submitted that the presently pending claims be reconsidered and allowed.

Rejection Under 35 U.S.C. § 103

The Examiner has rejected claims 1-21 as being obvious in view of the combination of Grissom, Toki, Dubowchik, and Habberfield. The Applicant respectfully submits that these claims are patentable over the cited references for the reasons set forth below as well as those set forth in earlier communications, and that the rejection should be withdrawn. The Applicant respectfully asserts the Examiner has not satisfied the requirements for establishing a case of *prima facie* obviousness in any of the § 103(a) rejections. The combination proposed by the Examiner would not make successful practice of the claimed invention obvious to one of ordinary skill in the art.

The Combination of Grissom, Toki, Dubowchik, and Habberfield

The Examiner has rejected claims 1-21 as being obvious over the combination of Grissom, Toki, Dubowchik, and Habberfield.

The present invention is directed to a conjugate of an anti-tumor drug and cobalamin or a derivative or analogue thereof, wherein these two molecules are joined at the 5'-OH of cobalamin by a linker that is cleavable by an intracellular enzyme. The present invention is also directed to such a conjugate where certain optional spacer molecules may be interposed in the bond between cobalamin and the linker, or the linker and the anti-tumor drug, or both. The invention as claimed accomplishes a number of objectives, including providing an anti-tumor drug in a form that is more easily (a) taken up enterally; (b) taken into cells by receptor-mediated endocytosis; and/or (c) released in an active form in the intracellular environment. This is due to a conjugate structure that allows important transport proteins (i.e. intrinsic factor and transcobalamin) to bind to cobalamin and therefore mediate transport of the conjugate across the gut wall and across cell membranes, and then allows intracellular enzymes to lyse the drug from the conjugate. The bringing together of the above objectives is a result of the claimed combination of elements, in the claimed arrangement, and this arrangement is accomplished by the reactions taught in the specification.

While the individual components of such molecules, or subgroups thereof, may be represented in the art, a *prima facie* case for obviousness requires that the prior art places the invention as a whole in the possession of the public. MPEP 2141.02. The soundness of a case for obviousness of a claimed compound may depend on whether the prior art renders obvious a method for making that compound, even if similar compounds exist in the prior art. MPEP 2144.09. Applicants respectfully submit that the Examiner has not demonstrated that the claimed invention is in the possession of the public based upon the asserted references, because these references do not show that the invention as a whole is disclosed in the prior art and they do not show one skilled in the art how to make the invention.

The asserted references do not teach the present invention as a whole

As the Examiner has stated, rebutting a *prima facie* case for obviousness is not based solely on the defects of individual references. However, to support a *prima facie* case for obviousness, the asserted references combined must disclose all of the elements of the claimed invention. The applicant asserts that each and every element is not present in the cited prior art.

The Grissom patent relates to fluorescent compounds that are covalently linked to a cobalamin and used as diagnostic and prognostic markers. While Grissom does teach a doxorubicin-cobalamin conjugate synthesized as a potential chemotherapeutic compound, that reference does not teach the structure of the doxorubicin-cobalamin conjugate. Grissom also fails to disclose the possibility of an enzyme-cleavable linker. As discussed above, the structure of the claimed invention is an important aspect in achieving the intended efficacy. This structure is the product of a combination of elements, including bonding configuration and the nature of the linker.

The Examiner has asserted Habberfield to provide the structure missing in the teaching of Grissom. However, the disclosure in Habberfield merely teaches the attachment of a therapeutic compound directly to a cobalamin derivative. It teaches further that a second derivative may be created by reacting the first derivative with a "functional linker." However, this use of the term "linker" is used only once in Habberfield, and in a very general sense, i.e. as part of a side-chain in a cobalamin derivative—not as providing an attachment designed to be cleavable in the intracellular environment, as required by the present invention. This is not surprising, as Habberfield is primarily concerned with enteral uptake and does not discuss at all the disposition of cobalamin conjugates after they are taken up by target cells. Therefore, it is clear that Habberfield, while teaching a cobalamin derivative and a therapeutic compound, fail to teach the linkers of the present invention.

The Examiner has asserted Dubowchik to provide a teaching of cathepsin B-cleavable linker, such as the cathepsin B-cleavable linker between the anti-tumor drug and cobalamin of the present invention. Dubowchik teaches stabilizing doxorubicin with an enzyme-cleavable peptide and a self-immolative PABC spacer. The peptide can be cleaved by cathepsin B so as to release the drug. However, despite the use of the term "linker" to refer to the peptides in Dubowchik, there is no teaching that these peptides are to be used to link doxorubicin to anything—the peptides are primarily

drug carriers that provide a stabilizing effect. In the present invention, enzyme-cleavable linkers must be suitable for linking an anti-tumor drug (and optionally a spacer) to the 5'-OH of a cobalamin or a derivative thereof. Dubowchik provides no teaching that the peptides disclosed therein would be suitable for the use required in the present invention.

The Examiner has also asserted Toki as teaching the attachment of self-immolative spacers and enzyme-cleavable linkers to anti-cancer drugs. Toki teaches a general method of activating anticancer drugs using proteases within solid tumors. Toki describes anticancer drugs that can be appended to a peptide, decreasing the toxicity of the anticancer drugs. Like Dubowchik, the peptide spacer in Toki is not itself used as a linker to another moiety as required by the present claims; rather, the peptide is a drug carrier. See Discussion, p. 1869. Once the drug-peptide complex enters a tumor cell, the cell's enzymes cleave the peptide and release the drug from the peptide. Furthermore, unlike the present invention, Toki does not teach the use of non-peptides at all. Therefore, Toki and Dubowchik are alike in failing to teach the use of peptides of the present invention, i.e. as an enzyme-cleavable linkage between an anti-tumor drug and cobalamin.

While a large number of peptides (or non-peptides) may be suitable for attachment to one of the disclosed moieties (an anti-tumor drug or a spacer), only some of these would be suitable for simultaneous attachment to the 5'-OH of a cobalamin in addition to providing a steric configuration that allows binding with transport proteins and cleavage by intracellular enzymes. While Grissom and Habberfield teach the use of cobalamin, they fail to teach the structural attachment of cobalamin to a drug as required in the present invention. Furthermore, while Toki and Dubowchik teach some of the elements of that attachment, they provide no suggestion that they should be incorporated with Grissom or Habberfield in a way that would yield the present invention. Therefore, Applicant submits that the asserted references do not demonstrate that the claimed invention as a whole is in possession of the public.

The asserted references do not provide a way to make the present invention

The asserted references also fail to render the present invention obvious because they do not provide (even in combination) a way to make the claimed

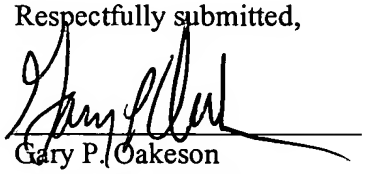
invention, or show that such a way is obvious. According to the present invention, peptide or non-peptide linkers must be specifically selected for their ability to link two moieties together (a cobalamin and an anti-tumor drug), which is not taught in any of the references. After suitable linkers are selected, the proper chemical reactions and conditions must be selected for attaching the linker at two (2) locations, one side to cobalamin and one side to an anti-tumor drug. Such a teaching—provided by the Applicants—is missing in the asserted references. In view of these references, one skilled in the art would therefore be faced with further modification and experimentation before reaching the present invention, while finding no teaching in those references for crossing that apparent gap in the art. Without such a teaching, the claimed structure is not *prima facie* obvious in view of the prior art, even if similar structures may be present in the prior art. MPEP 2144.09. For these reasons, as well as others set forth previously, Applicants submit that the Examiner has failed to make a *prima facie* case for obviousness of Applicants' invention.

In view of the foregoing, Applicants believe that claims 1-21 present allowable subject matter and allowance is respectfully requested. If any impediment to the allowance of these claims remains after consideration of the above remarks, and such impediment could be removed during a telephone interview, the Examiner is invited to telephone the undersigned attorney at (801) 566-6633 so that such issues may be resolved as expeditiously as possible.

Please charge any additional fees except for Issue Fee or credit any overpayment to Deposit Account No. 20-0100.

Dated this 3rd day of January, 2007.

Respectfully submitted,



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